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(54) Title: ACTIVE AGENT TRANSPORT SYSTEMS

(57) Abstract

(30) Priority Data:

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Methods for transporting a biologically active agent across a cellular membrane or a lipid bilayer. A first method includes the steps of: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to the native state and which is conformationally between the native and denatured states; (b) exposing the biologically active agent to a complexing perturbant to reversibly transform the biologically active agent to the intermediate state and to form a transportable supramolecular complex; and (c) exposing the membrane or bilayer to the supramolecular complex, to transport the biologically active agent across the membrane or bilayer. The perturbant has a molecular weight between about 150 and about 600 daltons, and contains at least one hydrophilic moiety and at least one hydrophobic moiety. The supramolecular complex comprises the perturbant non-covalently bound or complexed with the biologically active agent. In the present invention, the biologically active agent does not form a microsphere after interacting with the perturbant. A method for preparing an orally administrable biologically active agent comprising steps (a) and (b) above is also provided as are oral delivery compositions. Additionally, mimetics and methods for preparing mimetics are contemplated.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US98/20548

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :A61K 9/16; 9/50	
US CL: 424/451, 488, 489, 490, 491 According to International Patent Classification (IPC) or to both	national classification and IPC
B. FIELDS SEARCHED	
Minimum documentation searched (classification system follower	ed by classification symbols)
	or by Massindadon symbols
U.S. : 424/ 451, 488, 489, 490, 491	
Documentation searched other than minimum documentation to the NONE	e extent that such documents are included in the fields searched
Electronic data base consulted during the international search (of APS, CAS, MEDLINE, MEDLINE, BIOSIS, EMBASE	ame of data base and, where practicable, scarch terms used)
C. DOCUMENTS CONSIDERED TO BE RELEVANT	
Category* Citation of document, with indication, where an	propriate, of the relevant passages Relevant to claim No.
Y US 5,451,410 A (MILSTEIN et al document.	.) 19 Sept. 1995, see entire 1-111
Y US 5,578,323 A (MILSTEIN et al.) 2 document.	26 November 1996, see entire 1-111
Y US 5,443,841 A (MILSTEIN et al.) document.	22 August 1995, see entire 1-111
Further documents are listed in the continuation of Box (C. See patent family annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
to be of particular relevance "B" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be
"I." document which may throw doubts on priority claim(s) or which is cited to establish the publication data of another citation or other	considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be
**O" document referring to an oral disclosure, use, exhibition or other means	considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P" document published prior to the international filing data but later than the priority data claimed	"&" document member of the same patent family
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diluting said supramolecular complex.

IN THE CLAIMS:

1	 A method for delivering, by the subcutaneous route, a
2	biologically active agent to a subject in need of said biologically active agent,
3	said method comprising:
4	(a) providing a biologically active agent which can exist in a native
5	conformational state, a denatured conformational state, and an intermediate
6	conformational state which is reversible to said native state and is
7	conformationally between said native and denatured states;
8	(b) exposing said biologically active agent to a complexing perturbant
9	to reversibility transform said biologically active agent to said intermediate
10	state and to form a subcutaneously deliverable supramolecular complex,
11	said perturbant having a molecular weight between about
12	150 to about 600 daltons, and having at least one hydrophilic
13	moiety and at least one hydrophobic moiety,
14	said supramolecular complex comprising said perturbant
15	non-covalently complexed with said biologically active agent,
16	said biologically active agent not forming a microsphere
17	with said perturbant, and
18	said perturbant being present in an amount effective for
19	subcutaneous delivery of said biologically active agent; and
20	(c) subcutaneously administering said supramolecular complex to said
21	subject.
1	A method as defined in claim 1, further comprising
2	(d) after said administering step, removing said perturbant from
3	said supramolecular complex to transform said biologically active agent to said
4	native state.
1	 A method as defined in claim 2, wherein step (d) comprises

- 4. A method as defined in claim 1, wherein said intermediate
 state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles
 relative to said native state.
- 5. A method as defined in claim 1, wherein said biologically active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.
- A method as defined in claim 5, wherein said biologically-1 6. active agent is selected from the group consisting of human growth hormone, 2 bovine growth hormone, growth hormone-releasing hormone, an interferon, 3 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor, 4 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, 5 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, 6 vancomycin, desferrioxamine (DFO), or any combination of any of the 7 8 foregoing.
 - A method as defined in claim 1, wherein said perturbant comprises a proteinoid.
- 1 8. A method as defined in claim 1, wherein said perturbant is 2 selected from the group consisting of an acylated amino acid and an acylated 3 poly amino acid.
- 9. A method as defined in claim 1, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

1	A method as defined in claim 1, wherein said perturbant is
2	selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino acid.
1	11. A method as defined in claim 1, wherein said perturbant is
2	selected from the group consisting of an acylated ketone of an amino acid and
3	an acylated ketone of a poly amino acid.
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1	12. A method as defined in claim 1, wherein said perturbant
2	comprises a carboxylic acid having the formula
3	р со н
4	R—CO₂H
5	the state of the s
6	wherein R is C ₁ to C ₂₄ alkyl, C ₂ to C ₂₄ alkenyl, C ₃ to C ₁₀ cycloalkyl, C ₃
7	to C ₁₀ cycloalkenyl, phenyl, naphthyl, (C ₁ to C ₁₀ alkyl)phenyl, (C ₂ to C ₁₀
8	alkenyl)phenyl, (C ₁ to C ₁₀ alkyl)naphthyl, (C ₂ to C ₁₀ alkenyl)naphthyl,
9	phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and
10	naphthyl(C ₂ to C ₁₀ alkenyl);
11	R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1
12	to C_4 alkoxy, -OH, -SH, -CO ₂ R ¹ , C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl,
13	heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14	atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1
15	to C ₁₀)alkyl, or any combination thereof;
16	R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17	combination thereof; and
18	R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or
19	a salt thereof.
1	13. A method for preparing a subcutaneously deliverable
2	biologically active agent, said method comprising:
3	(a) providing a biologically active agent which can exist in a
	native conformational state a denatured conformational state, and an

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5	intermediate conformational state which is reversible to said native state and
6	is conformationally between said native and denatured states; and
7	(b) exposing said biologically active agent to a complexing
8	perturbant to reversibility transform said biologically active agent to said
9	intermediate state and to form a subcutaneously deliverable supramolecular
10	complex,
11	said perturbant having a molecular weight ranging from about
12	150 to about 600 daltons, and having at least one hydrophilic moiety
13	and at least one hydrophobic moiety,
14	said supramolecular complex comprising said perturbant
15	non-covalently complexed with said biologically active agent;
16	said biologically active agent not forming a microsphere with said
17	perturbant; and
18	said perturbant being present in an amount effective for
19	subcutaneous delivery of said biologically active agent.

- A method as defined in claim 13, wherein said intermediate state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.
- A method as defined in claim 13, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.
- A method as defined in claim 15, wherein said biologically-16. active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoletin, atrial naturetic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,

7	vancomycin, desferrioxamine (DFO), or any combination of any of the
8	foregoing.
1	17. A method as defined in claim 13, wherein said perturbant
2	comprises a proteinoid.
1	18. A method as defined in claim 13, wherein said perturbant
2	is selected from the group consisting of an acylated amino acid and an
3	acylated poly amino acid.
1	19. A method as defined in claim 13, wherein said perturbant
2	is selected from the group consisting of a sulfonated amino acid and a
3	sulfonated poly amino acid.
1	20. A method as defined in claim 13, wherein said perturbant
2	is selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino acid.
1	21. A method as defined in claim 13, wherein said perturbant
2	is selected from the group consisting of an acylated ketone of an amino acid
3	and an acylated ketone of a poly amino acid
1	22. A method as defined in claim 13, wherein said perturbant
2	comprises a carboxylic acid having the formula
3	
4	R—CO₂H
5	
6	wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3
7	to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}
8	alkenyi)phenyi, (C_1 to C_{10} alkyi)naphthyi, (C_2 to C_{10} alkenyi)naphthyi, phenyi(C_1
9	to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and

naphthyl(C_2 to C_{10} alkenyl);

PCT/US98/20548

11	R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1
12	to C ₄ alkoxy, -OH, -SH, -CO ₂ R ¹ , C ₃ to C ₁₀ cycloalkyl, C ₃ to C ₁₀ cycloalkenyl,
13	heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14	atoms of N, O, S or any combination thereof, aryl, (C1 to C10 alkyl)aryl, aryl(C1
15	to C ₁₀)alkyl, or any combination thereof;
16	R being optionally interrupted by oxygen, nitrogen, sulfur, or any

combination thereof; and

 R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or a salt thereof.

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- A subcutaneous delivery composition comprising a 23. supramolecular complex comprising:
- a biologically active agent in an intermediate 3 (a) conformational state non-covalently complexed with 4
 - a complexing perturbant having a molecular weight (b) ranging from about 150 to about 600 and having at least one hydrophilic moiety and at least one hydrophobic moiety;

wherein said intermediate state is reversible to said native state and is conformationally between a native conformational and a denatured conformational state of said biologically active agent and said composition is not a microsphere; and said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent.

- A composition as defined in claim 23, wherein said 1 24. biologically active agent is selected from the group consisting of a peptide, a 2 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination 3 4 of the foregoing.
- A composition as defined in claim 24, wherein said 25. 1 biologically-active agent is selected from the group consisting of human 2 growth hormone, bovine growth hormone, growth hormone-releasing 3 interferon, interleukin-II, insulin, heparin, calcitonin, 4 hormone, an

5	erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody,
6	somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7	vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8	combination of any of the foregoing.
1	26. A composition as defined in claim 23, wherein said
2	perturbant comprises a proteinoid.
1	27. A composition as defined in claim 23, wherein said
2	perturbant is selected from the group consisting of an acylated amino acid and
3	an acylated poly amino acid.
1	28. A composition as defined in claim 46, wherein said
2	perturbant is selected from the group consisting of a sulfonated amino acid
3	and a sulfonated poly amino acid.
1	29. A composition as defined in claim 23, wherein said
2	perturbant is selected from the group consisting of an acylated aldehyde of an
3	amino acid and an acylated aldehyde of a poly amino acid.
1	30. A composition as defined in claim 23, wherein said
2	perturbant is selected from the group consisting of an acylated ketone of an
3	amino acid and an acylated ketone of a poly amino acid.
1	31. A composition as defined in claim 23, wherein said
2	perturbant comprises a carboxylic acid having the formula
3	
4	R—CO₂H
5	
6	wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3
7	to C ₁₀ cycloalkenyl, phenyl, naphthyl, (C ₁ to C ₁₀ alkyl)phenyl, (C ₂ to C ₁₀
8	alkenyl)phenyl, (C ₁ to C ₁₀ alkyl)naphthyl, (C ₂ to C ₁₀ alkenyl)naphthyl, phenyl(C ₁

to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and 9 naphthyl(C₂ to C₁₀ alkenyl); 10 R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 11 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, 12 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more 13 atoms of N, O, S or any combination thereof, aryl, (C1 to C10 alkyl)aryl, aryl(C1 14 to C₁₀)alkyl, or any combination thereof; 15 R being optionally interrupted by oxygen, nitrogen, sulfur, or any 16 combination thereof; and 17 R1 is hydrogen, C1 to C4 alkyl or C2 to C4 alkenyl; or 18 a salt thereof. 19 A dosage unit form comprising: 32. 1 a composition as defined in claim 23; and 2 (A) an excipient, 3 (B) (a) a diluent, 4 (b) a disintegrant, (c) 5 a lubricant, (d) 6 a plasticizer, 7 (e) a colorant, (f) 8 a dosing vehicle, or 9 (g) any combination thereof. 10 (h)

33. A method for preparing an agent which is capable of being deliverable by the subcutaneous route to a subject in need of said agent, said method comprising:

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- (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;
- (b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said

10	intermediate state and to form a subcutaneously deliverable supramolecular
11	complex,
12	said perturbant having a molecular weight between about
13	150 and about 600 daltons, and having at least one hydrophilic moiety and
14	one hydrophilic moiety,
15	said supramolecular complex comprising said perturbant
16	non-covalently complexed with said biologically active agent,
17	said biologically active agent not forming a microsphere
18	with said perturbant, and
19	said perturbant being present in an amount effective for
20	subcutaneous delivery of said biologically active agent; and
21	(c) preparing a mimetic of said supramolecular complex.
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1	34. A method as defined in claim 33, wherein said biologically
2	active agent comprises a peptide and said mimetic comprises a peptide
3	mimetic.
1	35. A method for preparing an agent which is capable of being
2	delivered by the subcutaneous route to a subject in need of said agent, said
3	method comprising:
4	(a) providing a biologically active agent which can exist in a
5	native conformational state, a denatured conformational state, and an
6	intermediate which is reversible to said native state and is conformationally
7	between said native and denatured states;
8	(b) exposing said biologically active agent to a perturbant to
9	reversibly transform said biologically active agent to said intermediate state,
10	wherein said perturbant being present in an amount effective for subcutaneous
11	delivery of said biologically active agent; and
12	(c) preparing a mimetic of said intermediate state.

comprises a pH changing agent, an ionic strength changing agent, or guanidine hydrochloride. 37. A subcutaneous delivery composition comprising a mimetic of the subcutaneous delivery composition prepared by the method of claim 13. 38. A method for delivering, by the sublingual route, a biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to said subject.	1	36. A method as defined in claim 35, wherein said perturbant
37. A subcutaneous delivery composition comprising a mimetic of the subcutaneous delivery composition prepared by the method of claim 13. 38. A method for delivering, by the sublingual route, a biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	2	comprises a pH changing agent, an ionic strength changing agent, or
38. A method for delivering, by the sublingual route, a biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and	3	guanidine hydrochloride.
38. A method for delivering, by the sublingual route, a biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and		
1 38. A method for delivering, by the sublingual route, a 2 biologically active agent to a subject in need of said biologically active agent, 3 said method comprising: 4 (a) providing a biologically active agent which can exist in a 5 native conformational state, a denatured conformational state, and an 6 intermediate conformational state which is reversible to said native state and 7 is conformationally between said native and denatured states; 8 (b) exposing said biologically active agent to a complexing 9 perturbant to reversibility transform said biologically active agent to said 10 intermediate state and to form a subcutaneously deliverable supramolecular 11 complex, 12 said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic 14 moiety and at least one hydrophobic moiety, 15 said supramolecular complex comprising said perturbant 16 non-covalently complexed with said biologically active agent, 17 said biologically active agent not forming a microsphere with said 18 perturbant, and 19 said perturbant being present in an amount effective for 19 sublingual delivery of said biologically active agent; and 20 sublingually administering said supramolecular complex to	1	
biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and	2	of the subcutaneous delivery composition prepared by the method of claim 13.
biologically active agent to a subject in need of said biologically active agent, said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and		
said method comprising: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic molety and at least one hydrophobic molety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to		
1 (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to		•
native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	3	
intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	4	(a) providing a biologically active agent which can exist in a
is conformationally between said native and denatured states; (b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	5	native conformational state, a denatured conformational state, and an
9 perturbant to reversibility transform said biologically active agent to said 10 intermediate state and to form a subcutaneously deliverable supramolecular 11 complex, 12 said perturbant having a molecular weight between about 13 150 to about 600 daltons, and having at least one hydrophilic 14 moiety and at least one hydrophobic moiety, 15 said supramolecular complex comprising said perturbant 16 non-covalently complexed with said biologically active agent, 17 said biologically active agent not forming a microsphere with said 18 perturbant, and 19 said perturbant being present in an amount effective for 20 sublingual delivery of said biologically active agent; and 21 (c) sublingually administering said supramolecular complex to	6	intermediate conformational state which is reversible to said native state and
perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	7	is conformationally between said native and denatured states;
intermediate state and to form a subcutaneously deliverable supramolecular complex, said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	8	(b) exposing said biologically active agent to a complexing
said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and sublingually administering said supramolecular complex to	9	perturbant to reversibility transform said biologically active agent to said
said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	10	intermediate state and to form a subcutaneously deliverable supramolecular
150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	11	complex,
moiety and at least one hydrophobic moiety, said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	12	said perturbant having a molecular weight between about
said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and sublingually administering said supramolecular complex to	13	150 to about 600 daltons, and having at least one hydrophilic
non-covalently complexed with said biologically active agent, said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and sublingually administering said supramolecular complex to	14	moiety and at least one hydrophobic moiety,
said biologically active agent not forming a microsphere with said perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and sublingually administering said supramolecular complex to	15	said supramolecular complex comprising said perturbant
perturbant, and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	16	non-covalently complexed with said biologically active agent,
said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	17	said biologically active agent not forming a microsphere with said
said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and (c) sublingually administering said supramolecular complex to	18	perturbant, and
sublingual delivery of said biologically active agent; and sublingually administering said supramolecular complex to		·
21 (c) sublingually administering said supramolecular complex to		
		•
ZZ Said Subject.		
	~~	said subject.

- WO 99/16427 114 after said administering step, removing said perturbant from 2 (d) said supramolecular complex to transform said biologically active agent to said 3 4 native state. A method as defined in claim 39, wherein step (d) 1 40. comprises diluting said supramolecular complex. 2 A method as defined in claim 38, wherein said intermediate 1 41. state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles 2 3 relative to said native state. 42. A method as defined in claim 38, wherein said biologically 1 active agent is selected from the group consisting of a peptide, a 2
 - mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

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- 43. A method as defined in claim 42, wherein said biologicallyactive agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.
- A method as defined in claim 38, wherein said perturbant 1 44. 2 comprises a proteinoid.
- 1 A method as defined in claim 38, wherein said perturbant 45. is selected from the group consisting of an acylated amino acid and an 2 3 acylated poly amino acid.

1	46. A method as defined in claim 38, wherein said perturbant
2	is selected from the group consisting of a sulfonated amino acid and a
3	sulfonated poly amino acid.
1	47. A method as defined in claim 38, wherein said perturbant
2	is selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino acid.
1	48. A method as defined in claim 38, wherein said perturbant
2	is selected from the group consisting of an acylated ketone of an amino acid
3	and an acylated ketone of a poly amino acid.
1	49. A method as defined in claim 38, wherein said perturbant
2	comprises a carboxylic acid having the formula
3	
4	R—CO₂H
5	
6	wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3
7	to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}
8	alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl,
9	phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and
10	naphthyl(C ₂ to C ₁₀ alkenyl);
11	R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1
12	to C_4 alkoxy, -OH, -SH, -CO ₂ R ¹ , C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl,
13	heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14	atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1
15	to C ₁₀)alkyl, or any combination thereof;
16	R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17	combination thereof; and
18	R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or
19	a salt thereof.

WO 99/16427 PCT/US98/20548

1	50. A method for preparing a sublingually deliverable
2	biologically active agent, said method comprising:
3	(a) providing a biologically active agent which can exist in a native
4	conformational state, a denatured conformational state, and an intermediate
5	conformational state which is reversible to said native state and is
6	conformationally between said native and denatured states; and
7	(b) exposing said biologically active agent to a complexing perturbant
8	to reversibility transform said biologically active agent to said intermediate
9	state and to form a sublingually deliverable supramolecular complex,
10	said perturbant having a molecular weight ranging from about
11	150 to about 600 daltons, and having at least one hydrophilic moiety
12	and at least one hydrophobic moiety,
13	said supramolecular complex comprising said perturbant
14	non-covalently complexed with said biologically active agent;
15	said biologically active agent not forming a microsphere with said
16	perturbant; and
17	said perturbant being present in an amount effective for
18	sublingual delivery of said biologically active agent.
1	51. A method as defined in claim 50, wherein said intermediate
2	state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative
3	to said native state.
1	52. A method as defined in claim 50, wherein said biologically
2	active agent is selected from the group consisting of a peptide, a
3	micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4	of the foregoing.
1	53. A method as defined in claim 52, wherein said biologically-
2	active agent is selected from the group consisting of human growth hormone,
3	bovine growth hormone, growth hormone-releasing hormone, an interferon,
4	interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor,

WO 99/16427

5	an antigen, a monocional antibody, somatostatin, adichocordooriopin,
6	gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7	vancomycin, desferrioxamine (DFO), or any combination of any of the
8	foregoing,
1	54. A method as defined in claim 50, wherein said perturbant
2	comprises a proteinoid.
1	55. A method as defined in claim 50, wherein said perturbant
2	is selected from the group consisting of an acylated amino acid and an
3	acylated poly amino acid.
1	56. A method as defined in claim 50, wherein said perturbant
2	is selected from the group consisting of a sulfonated amino acid and a
3	sulfonated poly amino acid.
1	57. A method as defined in claim 50, wherein said perturbant
2	is selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino acid.
1	58. A method as defined in claim 50, wherein said perturbant
2	is selected from the group consisting of an acylated ketone of an amino acid
3	and an acylated ketone of a poly amino acid.
1	59. A method as defined in claim 50, wherein said perturbant
2	comprises a carboxylic acid having the formula
3	
4	R—CO₂H
5	
6	wherein R is C ₁ to C ₂₄ alkyl, C ₂ to C ₂₄ alkenyl, C ₃ to C ₁₀ cycloalkyl, C ₃ to
7	C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}
8	alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1

- to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and 9 10 naphthyl(C₂ to C₁₀ alkenyl); R being optionally substituted with C1 to C10 alkyl, C2 to C10 alkenyl, C1 11 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, 12 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more 13
- atoms of N, O, S or any combination thereof, aryl, (C1 to C10 alkyl)aryl, aryl(C1 14 15 to C₁₀)alkyl, or any combination thereof;
- R being optionally interrupted by oxygen, nitrogen, sulfur, or any 16 combination thereof; and 17
- R1 is hydrogen, C1 to C4 alkyl or C2 to C4 alkenyl; or 18 a salt thereof. 19

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- sublingual delivery composition comprising 60. Α supramolecular complex comprising:
 - a biologically active agent in an intermediate conformational state (a) non-covalently complexed with
 - a complexing perturbant having a molecular weight ranging from (b) about 150 to about 600 and having at least one hydrophilic moiety and at least one hydrophobic moiety;
 - wherein said intermediate state is reversible to said native state and is conformationally between a native conformational and a denatured conformational state of said biologically active agent and said composition is not a microsphere; and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent.
- A composition as defined in claim 60, wherein said 1 biologically active agent is selected from the group consisting of a peptide, a 2 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination 3 4 of the foregoing.
- A composition as defined in claim 61, wherein said 62. biologically-active agent is selected from the group consisting of human 2

3	growth hormone, bovine growth hormone, growth hormone-releasing
4	hormone, an interferon, interleukin-li, insulin, heparin, calcitonin,
5	erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody,
6	somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7	vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8	combination of any of the foregoing.
1	63. A composition as defined in claim 60, wherein said
2	perturbant comprises a proteinoid.
1	64. A composition as defined in claim 60, wherein said
2	perturbant is selected from the group consisting of an acylated amino acid and
3	an acylated poly amino acid.
1	65. A composition as defined in claim 60, wherein said
2	perturbant is selected from the group consisting of a sulfonated amino acid
3	and a sulfonated poly amino acid.
1	66. A composition as defined in claim 60, wherein said
2	perturbant is selected from the group consisting of an acylated aldehyde of an
3	amino acid and an acylated aldehyde of a poly amino acid.
1	67. A composition as defined in claim 60, wherein said
2	perturbant is selected from the group consisting of an acylated ketone of an
3	amino acid and an acylated ketone of a poly amino acid.
	CO A composition to defined in alaim 60 wherein spid
1	68. A composition as defined in claim 60, wherein said
2	perturbant comprises a carboxylic acid having the formula
3	B. CO.H.
4	R—CO₂H

6	wherein	R is C	$\mathrm{C_1}$ to $\mathrm{C_{24}}$ alkyl, $\mathrm{C_2}$ to $\mathrm{C_{24}}$ alkenyl, $\mathrm{C_3}$ to $\mathrm{C_{10}}$ cycloalkyl, $\mathrm{C_3}$ to
7	C ₁₀ cycloa	lkenyi,	phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}
8	alkenyl)phe	nyl, (C	C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_2
9	to C ₁₀ alk	yi), pi	nenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and
10	naphthyl(C	to C,	o alkenyl);
11	R bei	ng opt	tionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1
12	to C ₄ alkox	y, -OH	I, -SH, -CO $_2$ R 1 , C $_3$ to C $_{10}$ cycloalkyl, C $_3$ to C $_{10}$ cycloalkenyl,
13	heterocyclic	c havir	ng 3-10 ring atoms wherein the hetero atom is one or more
14	atoms of N,	0,50	or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1
15	to C ₁₀)alkyl	, or an	y combination thereof;
16		R bei	ng optionally interrupted by oxygen, nitrogen, sulfur, or any
17	combination	n there	eof; and
18		R¹ is	hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or
19		a sal	t thereof.
1		69.	A dosage unit form comprising:
2	(A)	a cor	nposition as defined in claim 60; and
3	(B)	(a)	an excipient,
4		(b)	a diluent,
5		(c)	a disintegrant,
6		(d)	a lubricant,
7		(e)	a plasticizer,
8		(f)	a colorant,
9		(g)	a dosing vehicle, or
10		(h)	any combination thereof.
1		70.	A method for preparing an agent which is capable of being
2	administere	d by th	ne sublingual route to a subject in need of said agent, said
3	method con	nprisin	g:
4	(a)	provi	ding a biologically active agent which can exist in a native
5	conformatio	nal sta	ate, a denatured conformational state, and an intermediate

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- conformational state which is reversible to said native state and is conformationally between said native and denatured states;

 (b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a sublingually administrable supramolecular complex,
 - said perturbant having a molecular weight between about 150 and about 600 daltons, and having at least one hydrophilic moiety and one hydrophilic moiety,
- said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,
- said biologically active agent not forming a microsphere with said perturbant; and
 - said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and
 - (c) preparing a mimetic of said supramolecular complex.
- 1 71. A method as defined in claim 70, wherein said biologically 2 active agent comprises a peptide and said mimetic comprises a peptide 3 mimetic.
 - 72. A method for preparing an agent which is capable of being administered by the sublingual route to a subject in need of said agent, said method comprising:
 - (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate which is reversible to said native state and is conformationally between said native and denatured states;
 - (b) exposing said biologically active agent to a perturbant to reversibly transform said biologically active agent to said intermediate state, wherein said perturbant is in an amount effective for sublingual delivery of said biologically active agent; and
- 12 (c) preparing a mimetic of said intermediate state.

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1	73. A method as defined in claim 72, wherein said perturbant
2	comprises a pH changing agent, an ionic strength changing agent, or
3	guanidine hydrochloride.
1	74. An oral delivery composition comprising a mimetic of the
2	oral delivery composition prepared by the method of claim 50.
1	75. A method for delivering, by the intranasal route, a
2	biologically active agent to a subject in need of said biologically active agent,
3	said method comprising:
4	(a) providing a biologically active agent which can exist in a native
5	conformational state, a denatured conformational state, and an intermediate
6	conformational state which is reversible to said native state and is
7	conformationally between said native and denatured states;
8	(b) exposing said biologically active agent to a complexing perturbant
9	to reversibility transform said biologically active agent to said intermediate
10	state and to form an intranasally administrable supramolecular complex,
11	said perturbant having a molecular weight between about
12	150 to about 600 daltons, and having at least one hydrophilic
13	moiety and at least one hydrophobic moiety,
14	said supramolecular complex comprising said perturbant
15	non-covalently complexed with said biologically active agent,
16	said biologically active agent not forming a microsphere
17	with said perturbant, and
18	said perturbant being present in an amount effective for
19	intranasal delivery of said biologically active agent; and
20	(c) intranasally administering said supramolecular complex to said
21	subject.

A method as defined in claim 75, further comprising

- after said administering step, removing said perturbant from 2 (d) said supramolecular complex to transform said biologically active agent to said 3 4 native state.
- A method as defined in claim 76, wherein step (d) 77. 1 2 comprises diluting said supramolecular complex.
- A method as defined in claim 75, wherein said intermediate 78. 1 state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles 2 relative to said native state. 3
- A method as defined in claim 75, wherein said biologically 1 79. 2 active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination 3 4 of the foregoing.
- A method as defined in claim 79, wherein said biologically-80. active agent is selected from the group consisting of human growth hormone, 2 bovine growth hormone, growth hormone-releasing hormone, an interferon, 3 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor, 4 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, 6 vancomycin, desferrioxamine (DFO), or any combination of any of the 7 foregoing.

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- A method as defined in claim 75, wherein said perturbant 1 81. 2 comprises a proteinoid.
- A method as defined in claim 75, wherein said perturbant 82. 1 is selected from the group consisting of an acylated amino acid and an 2 3 acylated poly amino acid.

1	83. A method as defined in claim 75, wherein said perturbant
2	is selected from the group consisting of a sulfonated amino acid and a
3	sulfonated poly amino acid.
1	84. A method as defined in claim 75, wherein said perturbant
2	is selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino.
1	85. A method as defined in claim 75, wherein said perturbant
2	is selected from the group consisting of an acylated ketone of an amino acid
3	and an acylated ketone of a poly amino acid.
1	86. A method as defined in claim 75, wherein said perturbant
2	comprises a carboxylic acid having the formula
3	
4	R—CO₂H
5	
6	wherein R is C ₁ to C ₂₄ alkyl, C ₂ to C ₂₄ alkenyl, C ₃ to C ₁₀ cycloalkyl, C ₃ to
7	C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}
8	alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1
9	to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and
0	naphthyl(C ₂ to C ₁₀ alkenyl);
1	R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1
2	to C_4 alkoxy, -OH, -SH, -CO ₂ R ¹ , C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl,
3	heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
4	atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1
5	to C ₁₀)alkyl, or any combination thereof;
6	R being optionally interrupted by oxygen, nitrogen, sulfur, or any
7	combination thereof; and
8	R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or
9	a salt thereof.

1	87. A method for preparing an intranasally deliverable
2	biologically active agent, said method comprising:
3	(a) providing a biologically active agent which can exist in a native
4	conformational state, a denatured conformational state, and an intermediate
5	conformational state which is reversible to said native state and is
6	conformationally between said native and denatured states; and
7	(b) exposing said biologically active agent to a complexing perturbant
8	to reversibility transform said biologically active agent to said intermediate
9	state and to form an intranasally administrable supramolecular complex,
10	said perturbant having a molecular weight ranging from about
11	150 to about 600 daltons, and having at least one hydrophilic moiety
12	and at least one hydrophobic molety,
13	said supramolecular complex comprising said perturbant
14	non-covalently complexed with said biologically active agent; and
15	said biologically active agent not forming a microsphere with said
16	perturbant;
17	said perturbant being present in an amount effective for intranasal
18	delivery of said biologically active agent.
1	88. A method as defined in claim 87, wherein said intermediate
2	state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative
3	to said native state.
1	89. A method as defined in claim 87, wherein said biologically
2	active agent is selected from the group consisting of a peptide, a
3	micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4	of the foregoing.
1	90. A method as defined in claim 89, wherein said biologically-
2	active agent is selected from the group consisting of human growth hormone,
3	bovine growth hormone, growth hormone-releasing hormone, an interferon,
4	interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor,

WO 99/16427 PCT/US98/20548

5	an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin
3	gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium
7	vancomycin, desferrioxamine (DFO), or any combination of any of the
3	foregoing.
ì	91. A method as defined in claim 87, wherein said perturbant
2	comprises a proteinoid.
	and the defined in plain 97 wherein and porturbant
1	92. A method as defined in claim 87, wherein said perturbant
2	is selected from the group consisting of an acylated amino acid and an
3	acylated poly amino acid.
ı	93. A method as defined in claim 87, wherein said perturbant
2	is selected from the group consisting of a sulfonated amino acid and a
3	sulfonated poly amino acid.
,	Sanonated poly allimo delet
1	94. A method as defined in claim 87, wherein said perturbant
2	is selected from the group consisting of an acylated aldehyde of an amino acid
3	and an acylated aldehyde of a poly amino acid.
1	95. A method as defined in claim 87, wherein said perturbant
2	is selected from the group consisting of an acylated ketone of an amino acid
3	and an acylated ketone of a poly amino acid.
1	96. A method as defined in claim 87, wherein said perturbant
2	comprises a carboxylic acid having the formula
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4	R—CO₂H
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6	wherein R is C ₁ to C ₂₄ alkyl, C ₂ to C ₂₄ alkenyl, C ₃ to C ₁₀ cycloalkyl, C ₃ to
7	C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10}

alkenyl)
phenyl, (C $_{\rm 10}$ alkyl)naphthyl, (C $_{\rm 2}$ to C $_{\rm 10}$ alkenyl)
naphthyl, phenyl(C $_{\rm 1}$

- to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and 9 10 naphthyl(C2 to C10 alkenyl); R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 11 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, 12 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more 13 atoms of N, O, S or any combination thereof, aryl, (C1 to C10 alkyl)aryl, aryl(C1 14 to C₁₀)alkyl, or any combination thereof; 15 R being optionally interrupted by oxygen, nitrogen, sulfur, or any 16 17 combination thereof; and R1 is hydrogen, C1 to C4 alkyl or C2 to C4 alkenyl; or 18 19 a salt thereof. intranasal delivery composition comprising a 1 97. An 2 supramolecular complex comprising: a biologically active agent in an intermediate conformational state 3 (a) 4 non-covalently complexed with a complexing perturbant having a molecular weight ranging from 5 about 150 to about 600 and having at least one hydrophilic moiety and at 6 7 least one hydrophobic moiety; wherein said intermediate state is reversible to said native state 8 and is conformationally between a native conformational and a denatured 9 conformational state of said biologically active agent and said composition is 10 not a microsphere; and said perturbant being present in an amount effective 11 12 for intranasal delivery of said biologically active agent. 1 98.
- 1 98. A composition as defined in claim 97, wherein said 2 biologically active agent is selected from the group consisting of a peptide, a 3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination 4 of the foregoing.
 - 99. A composition as defined in claim 98, wherein said biologically-active agent is selected from the group consisting of human

3	growth hormone, bovine growth hormone, growth hormone-releasing
4	hormone, an interferon, interleukin-II, insulin, heparin, calcitonin,
5	erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody,
6	somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7	vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8	combination of any of the foregoing.
1	100. A composition as defined in claim 97, wherein said
2	perturbant comprises a proteinoid.
1	101. A composition as defined in claim 97, wherein said
2	perturbant is selected from the group consisting of an acylated amino acid and
3	an acylated poly amino acid.
1	102. A composition as defined in claim 97, wherein said
2	perturbant is selected from the group consisting of a sulfonated amino acid
3	and a sulfonated poly amino acid.
1	103. A composition as defined in claim 97, wherein said
2	perturbant is selected from the group consisting of an acylated aldehyde of an
3	amino acid and an acylated aldehyde of a poly amino acid.
	•
1	104. A composition as defined in claim 97, wherein said
2	perturbant is selected from the group consisting of an acylated ketone of an
3	amino acid and an acylated ketone of a poly amino acid.
1	105. A composition as defined in claim 97, wherein said
2	perturbant comprises a carboxylic acid having the formula
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4	R—CO₂H
5	

WO 99/16427 PCT/US98/20548

6 wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to 7 C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 8 9 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and 10 naphthyl(C2 to C10 alkenyl); 11 R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, - CO_2R^1 , C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, 12 13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more 14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof; 15 16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any 17 combination thereof; and R1 is hydrogen, C1 to C4 alkyl or C2 to C4 alkenyl; or 18 19 a salt thereof. 1 106. A dosage unit form comprising: 2 (A) a composition as defined in claim 97; and 3 (B) (a) an excipient, 4 (b) a diluent, 5 (c) a disintegrant, 6 (d) a lubricant, 7 (e) a plasticizer, 8 (f) a colorant, 9 (g) a dosing vehicle, or 10 (h) any combination thereof.

107. A method for preparing an agent which is capable of being administered by the intranasal route to a subject in need of said agent, said method comprising:

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(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate

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to reversibly transform said biologically active agent to said intermediate state and to form an intranasally administrable supramolecular complex,

said perturbant having a molecular weight between about 150 and about 600 daltons, and having at least one hydrophilic moiety and one hydrophilic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

said biologically active agent not forming a microsphere with said perturbant, and

said perturbant being present in an amount effective for intranasal delivery of said biologically active agent; and

- preparing a mimetic of said supramolecular complex. (c)
- 108. A method as defined in claim 107, wherein said biologically 1 active agent comprises a peptide and said mimetic comprises a peptide 2 mimetic. 3
 - 109. A method for preparing an agent which is capable of being administered by the intranasal route to a subject in need of said agent, said method comprising:
 - providing a biologically active agent which can exist in a native (a) conformational state, a denatured conformational state, and an intermediate which is reversible to said native state and is conformationally between said native and denatured states;
 - exposing said biologically active agent to a perturbant to (b) reversibly transform said biologically active agent to said intermediate state, wherein said perturbant is in an amount effective for intranasal delivery of said biologically active agent; and
 - preparing a mimetic of said intermediate state. (c)

- 1 110. A method as defined in claim 109, wherein said perturbant 2 comprises a pH changing agent, an ionic strength changing agent, or 3 guanidine hydrochloride.
- 1 111. An oral delivery composition comprising a mimetic of the oral delivery composition prepared by the method of claim 87.